

Serial No.: 09/653,730

-8-

Group Art Unit: 1645

REMARKS

The remarks presented herein are responsive to the Final Office Action dated June 3, 2003 (Paper No. 12).

Applicants and their Attorney would like to thank the Examiner for the courtesy of the telephonic interview of September 2, 2003, during which the foregoing claim amendments were discussed.

Claims 1, 3-26, and 75 were pending in this application. Claims 1, 7, 9, 21, 24, 25, and 26 have been amended and new claims 76, 77, 78, 79, 80, 81 and 82 have been added. Accordingly, claims 1, 3-26, and 75-82 will remain pending in the application upon entry of the claim amendments presented herein.

Support for the amendments to the claims and for the new claims may be found throughout the specification, including the originally filed claims. In particular, support for new claim 76 may be found at, for example, page 47, lines 17-24 and at page 22, lines 21-22 of Applicants' specification. Support for new claim 77 may be found at, for example, page 5, line 36 through page 7, line 7 of Applicants' specification. Support for new claims 78-81 may be found at, for example, page 18, lines 22-37 of Applicants' specification.

Support for the amendments to claim 1 may be found at, for example, page 6, lines 4-5 and lines 20-21, and page 22, lines 15-18 of Applicants' specification. The amendment to claim 1 requires that the test compound be a molecule other than the quorum sensing signal molecule. Applicants' specification discloses, in several instances, methods for identifying a modulator of quorum sensing signaling in bacteria by contacting a cell with a quorum sensing molecule *in the presence and absence of a test compound*. Because the quorum sensing molecule may be present at the same time the test compound is present, it is clear that the quorum sensing molecule cannot be the same molecule as the test compound. As set forth in the M.P.E.P., "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement" (M.P.E.P. §2163.02). Thus, it is clear based on the foregoing teachings in Applicants' specification, that Applicants were in possession of the invention set forth in amended claim 1.

No new matter has been added. Amendment of the claims should in no way be construed as an acquiescence to any of the objections/rejections set forth in the instant Office Action, and

Serial No.: 09/653,730

-9-

Group Art Unit: 1645

was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or one or more separate applications.

Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's indication that the rejection of claims 1-26 under 35 U.S.C. §112, first paragraph and the rejection of claims 1-26 under 35 U.S.C. §112, second paragraph, as set forth in the Office Action dated September 19, 2002, have been withdrawn.

Election/Restrictions

With respect to claim 75, the Examiner is of the opinion that

[n]ewly submitted claim 75 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claim is drawn to a method of: identifying a modulator of quorum sensing signaling comprising SEQ ID NO:1-36. The inventions are distinct, each from the other because the methods rely upon the nucleotide sequences selected from SEQ ID NO:1-36 which are distinct physically and structurally; and are therefore patentably distinct, each group from the other, and one sequence is not required to practice the other. Each group comprises separate and distinct nucleotide sequences that do not share a substantial structural feature disclosed as being essential to the utility of the invention. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 75 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants respectfully submit that claim 75 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, comprising providing a cell which comprises a quorum sensing controlled gene wherein the quorum sensing controlled gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1-36, operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with a quorum sensing signal molecule in the presence and absence of a test

Serial No.: 09/653,730

-10-

Group Art Unit: 1645

compound; and comparing the detectable signal generated in the presence and absence of a test compound.

Applicants respectfully submit that generic claim 1, which is directed to a method for identifying a modulator of quorum sensing signaling in bacteria by providing a cell which endogenously synthesizes a quorum sensing signal molecule, wherein said cell comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to the quorum sensing signal molecule; contacting said cell with a test compound; and comparing the detectable signal generated in the presence and absence of a test compound, includes methods for identifying a modulator of quorum sensing signaling wherein the quorum sensing controlled gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1-36. Furthermore, the patentability of claim 75 does not depend upon the patentability of these sequences since Applicants are not claiming the compositions comprising the sequences themselves, but rather a method which utilizes these sequences. Claim 1 has already been examined by the Examiner. Therefore, Applicants respectfully submit that examination of claim 75 does not present an undue burden to the Examiner.

However, in the interview conducted on September 2, 2003 between Applicants' attorney and Examiner Hines regarding the instant application, the Examiner agreed to allow a species election of a single nucleotide sequence, for search purposes only.

It is Applicants' understanding that under 35 U.S.C. §121, an election of a single species for prosecution on the merits is required, to which the claims will be restricted if no generic claim is finally held allowable. Applicants submit that claim 1 is generic. Accordingly, Applicants elect under 35 U.S.C. §121, with traverse, **SEQ ID NO:2**, as the species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently claim 1 is readable on this species. It is Applicants' understanding that the search will be extended to the remaining species upon a finding of allowability. Applicants further understand that upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent from or otherwise include all the limitations of an allowed generic claims as provided by 37 C.F.R. §1.41 *et seq.*

Serial No.: 09/653,730

-11-

Group Art Unit: 1645

Claim Objections

The Examiner has objected to claims 3, 7, 9, 17, 21 24, 25 and 26 because, according to the Examiner, "the claims depend upon non-elected claim 75."

Applicants respectfully submit that, as set forth above, the Examiner has indicated that the above restriction is to be considered a species election requirement. Applicants have elected a single sequence, for search purposes only. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing objection to claims 3, 7, 9, 17, 21 24, 25 and 26.

Rejection of Claims 1, 3-7, 9-10, 13-15 and 17-26 Under 35 U.S.C. §102(b)

The Examiner has maintained the rejection of claims 1, 3-7, 9-10, 13-15 and 17-26 under 35 U.S.C. §102(b) as being anticipated by Pearson *et al.* (*J. of Bacteriol* (1997) 179(18): 5756-5767) "for reasons already of record." In particular, the Examiner is of the opinion that

[t]he rejection was on the grounds that Pearson *et al.* teach a method for identifying a modulator of quorum sensing signaling in bacteria, comprising the claimed steps. Applicants assert that Pearson *et al.*, do not teach or suggest the method for identifying a modulator because Pearson *et al.*, utilizes a *P. aeruginosa* *lasI* *rhII* double-mutant that cannot endogenously produce a quorum sensing signal molecule. However it is [the] examiner's position that the claims only require a cell which is capable of endogenously synthesizing a quorum sensing signal, therefore, the cell does not have to actually be able to synthesize a quorum sensing signal. Furthermore, applicant points to one mutant that Pearson *et al.*, teach. However Pearson *et al.*, teach several other cells which would be capable of endogenously producing a quorum sensing signal. Thus the fact that one cell would not be capable of synthesis does not teach away from the other cells that would be capable of said synthesis. Therefore applicants' argument to that one example is not persuasive, when the prior art teaches other capable examples.

Applicants respectfully traverse the foregoing rejection under 35 U.S.C. §102(b) for the following reasons.

For the Examiner's convenience, a general description of the quorum sensing pathway is being provided below.

Description of Quorum Sensing

As set forth in Applicants' specification at page 11, line 28 through page 12, line 29, *Pseudomonas aeruginosa* has two quorum sensing systems, referred to as the *las* system and the *rhl* system. In gram negative bacteria, such as *Pseudomonas aeruginosa*, quorum sensing involves two proteins, the autoinducer synthase – referred to as the I protein – and the transcriptional activator – referred to as the R protein. In the *las* system of *Pseudomonas aeruginosa*, the I protein is *lasI* and the transcriptional activator is *lasR*. In the *rhl* system of *Pseudomonas aeruginosa*, the I protein is *rhlI* and the transcriptional activator is *rhlR*.

The autoinducer synthase (the I protein, i.e., *LasI* or *RhlI*) produces a quorum sensing signal molecule which is an acylated homoserine lactone (the "autoinducer"), which can diffuse into the surrounding environment (Fuqua, C. *et al* (1998) *Curr Opin Microbiol.* 1(2):183-189; Fuqua, *et al.* 1994. *J Bacteriol.* 176(2):269-75). The quorum sensing signal molecule produced in the *las* system is 3-oxo-dodecanoyl-HSL (3-oxo-C12-HSL, referred to in the Pearson *et al.* reference as PAI-1), while the quorum sensing signal molecule produced in the *rhl* system is butanoyl-HSL (C4-HSL, referred to in the Pearson *et al.* reference as PAI-2). Once the concentration of the quorum sensing signal molecule (i.e., PAI-1 or PAI-2) reaches a defined threshold, it binds to the R protein (i.e., *LasR* or *RhlR*) which then activates transcription of numerous genes. Appendix A, attached hereto for the Examiner's convenience, contains a schematic illustration of the quorum sensing pathway.

Pearson *et al*

Pearson *et al* investigates the roles of the *rhl* and *las* quorum sensing systems in the expression of certain virulence genes, e.g., the rhamnolipid biosynthesis operon *rhlAB* and *lasB*. Pearson *et al.* describes the use of mutant strains of bacteria, including mutant strains of *Pseudomonas aeruginosa*, which are unable to produce a quorum sensing signal molecule. The mutant strain contains a reporter gene and a transcriptional activator. PAI-1 and PAI-2, the quorum sensing signal molecules (which are the endogenously produced autoinducers of *las* and

Serial No.: 09/653,730

-13-

Group Art Unit: 1645

rhl systems in *Pseudomonas aeruginosa*) were exogenously added and the reporter gene was monitored. Pearson *et al.* showed that PAI-2, the quorum sensing signal molecule, is required for expression of *rhlAB*, and that PAI-2 interacts with RhlR to induce *rhlA* expression. Pearson *et al.* also teach that PAI-1 does not significantly activate RhlR to induce either *rhlA* or *lasB* expression, indicating that RhlR has high specificity for its cognate autoinducer, PAI-2 (see page 5762, last two paragraphs of second column and first paragraph of page 5763, and page 5765, first paragraph).

Pending claim 1 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising providing a cell which is capable of endogenously synthesizing a quorum sensing signal molecule, wherein said cell comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to the quorum sensing signal molecule; contacting said cell with a test compound, *wherein the test compound is other than said quorum sensing signal molecule*; and comparing said detectable signal generated in the presence of said test compound with said detectable signal generated in the absence of said test compound, to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

New claim 76 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with 3-oxo-C12 homoserine lactone *in the presence and absence of a test compound*; and comparing said detectable signal generated in the presence of said test compound with said detectable signal generated in the absence of said test compound, to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

New claim 77 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with said quorum sensing signal molecule *in the presence and absence of a test compound*; and detecting

Serial No.: 09/653,730

-14-

Group Art Unit: 1645

a change in said detectable signal to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

For a prior art reference to anticipate a claimed invention in terms of 35 U.S.C. §102, the prior art must teach *each and every element* of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that Pearson *et al.* fail to teach each and every limitation of claims 1, 76, and 77. As set forth above, the main focus of the Pearson *et al.* reference is to characterize the quorum sensing signaling pathway including the roles of the *rhl* and *las* quorum sensing systems in the expression of certain virulence genes. Pearson *et al.* study the expression of genes in the presence of certain quorum sensing signaling molecules (e.g., PAI-2). The presently claimed invention is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, wherein a test compound is added *and wherein the test compound is other than said quorum sensing signal molecule*, or contacting said cell with said quorum sensing signal molecule *in the presence and absence of a test compound*. Therefore, the pending claims require that, in addition to the quorum sensing signal molecule, a test compound is added. Pearson *et al.* do not teach or suggest the use of any test compound to identify a modulator of quorum sensing signaling, and, thus, do not teach or suggest each and every element of the claimed invention.

Furthermore, Applicants respectfully submit that although cells, e.g., wild type *P. aeruginosa* cells are known to endogenously synthesize a quorum sensing signal, Pearson, *et al.* do not teach or suggest using a cell which endogenously synthesizes a quorum sensing signal *in an assay to identify a modulator of quorum sensing signaling*, as is set forth in the claimed invention. Therefore, Pearson *et al.* do not teach or suggest each and every element of the claimed invention.

Moreover, Pearson *et al.* fails to teach or suggest each and every limitation of claim 75 as Pearson *et al.* does not teach or suggest a method for identifying a modulator of quorum sensing signaling in bacteria, comprising providing a cell which comprises a quorum sensing controlled gene wherein the quorum sensing controlled gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1-36.

Serial No.: 09/653,730

-15-

Group Art Unit: 1645

Accordingly, for the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection under 35 U.S.C. §102(b).

Rejection of Claims 8, 11-12, and 16 Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 8, 11-12, and 16 under 35 U.S.C. §103(a) as being unpatentable over Pearson *et al.* (*J of Bacteriol.* (1997) 179(18): 5756-5767) in view of Passador *et al.* (*Science*, 1993. 260:1127-1130) "for reasons already of record." In particular, the Examiner is of the opinion that "the rejection was on the grounds that it would have been *prima facie* obvious at the time of applicants invention to modify the method for identifying a modulator of quorum sensing signaling in bacteria comprising the recited steps as taught by Pearson *et al.*, to include a second cell that produces the quorum sensing signal molecule, instead of adding the molecule to the cell."

Furthermore, the Examiner is of the opinion that

[i]n response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one would have a reasonable expectation of success in using a second cell to produce the molecule since Passador *et al.*, teach that the expression of *P. aeruginosa* virulence genes requires cell-to-cell communication whereby one cell produces the molecule and the other cell can respond to the production of the molecule. Applicants argument that Pearson *et al.*, in view of Passador *et al.*, do not teach or suggest a cell which is capable of endogenously synthesizing a quorum sensing signal because Pearson *et al.*, utilizes a *P. aeruginosa lasI rhII* double-mutant which cannot endogenously produce a quorum sensing signal molecule, is not persuasive for the reasons previously stated.

Applicants respectfully traverse the foregoing rejection for the following reasons. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the

Serial No.: 09/653,730

-16-

Group Art Unit: 1645

art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). **Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations** (M.P.E.P. 2143).

Claim 7 has been amended such that it is no longer dependent upon claim 1, and therefore claims 8, 11-12, and 16 are no longer dependent upon claim 1. Claim 7 is however dependent up on claims 75, 76, and 77. Claim 75 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a quorum sensing controlled gene wherein said quorum sensing controlled gene comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs:1-36, operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with said quorum sensing signal molecule in the presence and absence of a test compound; and comparing said detectable signal generated in the presence of said test compound with said detectable signal generated in the absence of said test compound, to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

New claim 76 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with 3-oxo-C12 homoserine lactone **in the presence and absence of a test compound**; and comparing said detectable signal generated in the presence of said test compound with said detectable signal

Serial No.: 09/653,730

-17-

Group Art Unit: 1645

generated in the absence of said test compound, to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

New claim 77 is directed to a method for identifying a modulator of quorum sensing signaling in bacteria, said method comprising: providing a cell which comprises a regulatory sequence of a quorum sensing controlled gene operatively linked to a gene that generates a detectable signal in response to a quorum sensing signal molecule; contacting said cell with said quorum sensing signal molecule *in the presence and absence of a test compound*; and detecting a change in said detectable signal to thereby identify said test compound as said modulator of quorum sensing signaling in bacteria.

As set forth above, the primary reference of Pearson *et al.* fails to teach or suggest a method for identifying a modulator of quorum sensing signaling in bacteria comprising contacting said cell with said quorum sensing signal molecule *in the presence and absence of a test compound*, as is required by claims 76 and 77, and claims depending therefrom, including claims 8, 11-12, and 16. Furthermore, Pearson *et al.* do not teach or suggest a method for identifying a modulator of quorum sensing signaling in bacteria using a cell comprising a specific nucleotide sequence selected from the group consisting of SEQ ID NO:1-SEQ ID NO:36, as is required by new claim 75 and claims depending therefrom.

Moreover, the secondary reference of Passador *et al.* fails to cure the deficiencies in the teachings of the Pearson *et al.* reference. Specifically, Passador *et al.* does not teach or suggest a method for identifying a modulator of quorum sensing signaling in bacteria comprising contacting said cell with said quorum sensing signal molecule *in the presence and absence of a test compound*, as is required by claims 76 and 77 and claims depending therefrom, including claims 8, 11-12, and 16. Furthermore, Passador *et al.* do not teach or suggest a method for identifying a modulator of quorum sensing signaling in bacteria using a cell comprising a specific nucleotide sequence selected from the group consisting of SEQ ID NO:1-SEQ ID NO:36, as is required by claim 75, and claims depending therefrom.

In view of the foregoing, Applicants respectfully submit that the combination of Pearson *et al.* and Passador *et al.* fail to teach or suggest Applicants' invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw rejection of the pending claims under 35 U.S.C. §103.

Serial No.: 09/653,730

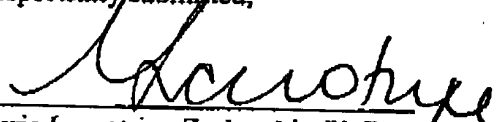
-18-

Group Art Unit: 1645

SUMMARY

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



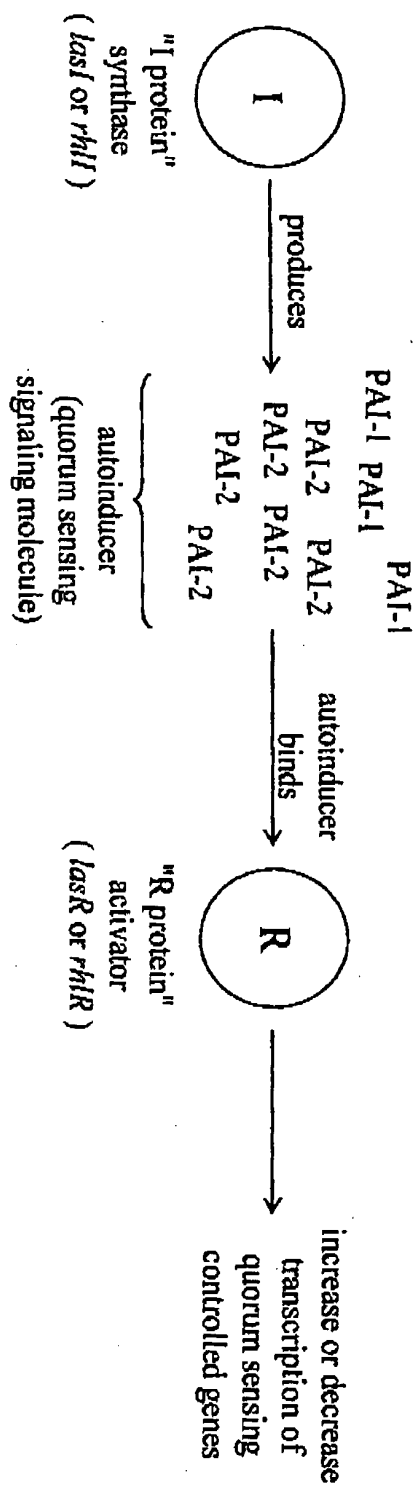
Maria Laccotripe Zacharakis, Ph.D., J.D.
Limited Recognition Under 37 C.F.R. 10.9(b)
Attorney for Applicant

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: October 3, 2003

Appendix A

Quorum Sensing Signaling System



PTO/SB/22 (08-03)

Approved for use through 7/31/2008 OMB 0651-0031

U S Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1985, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)		Docket No. (Optional) UIZ-038	
In re Application of Marvin Whiteley, et al			
Application Number 09/853730-Conf. #5801		Filed September 1, 2000	
For QUORUM SENSING SIGNALING IN BACTERIA			
Art Unit 1645		Examiner J. Hines	

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

<input checked="" type="checkbox"/>	One month (37 CFR 1.17(a)(1))	\$ <u>110.00</u>
<input type="checkbox"/>	Two months (37 CFR 1.17(a)(2))	\$ _____
<input type="checkbox"/>	Three months (37 CFR 1.17(a)(3))	\$ _____
<input type="checkbox"/>	Four months (37 CFR 1.17(a)(4))	\$ _____
<input type="checkbox"/>	Five months (37 CFR 1.17(a)(5))	\$ _____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: \$ 55.00

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 12-0080.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.


☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☐ attorney or agent of record. Registration Number _____

☒ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) LRA

October 3, 2003
Date

(617) 227-7400
Telephone Number


Signature

Maria Lacompe Zacharakis, Ph.D.
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of 1 forms are submitted.

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office, facsimile no. (703) 872-9307, on the date shown below

Dated: October 3, 2003

Signature

(Maria Zaccarias Zacharakis, Ph.D.)

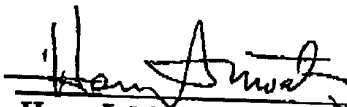
**BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATE PATENT AND TRADEMARK OFFICE**

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Maria C. Laccotripe Zacharakis is hereby given limited recognition under 37 CFR §10.9(b) as an employee of Lahive & Cockfield, LLP, to prepare and prosecute patent applications where the patent applicant is the client of Lahive & Cockfield, LLP, and the attorney or agent of record in the applications is a registered practitioner who is a member of the Lahive & Cockfield, LLP. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Maria C. Laccotripe Zacharakis ceases to lawfully reside in the United States, (ii) Maria C. Laccotripe Zacharakis' employment with Lahive & Cockfield, LLP ceases or is terminated, or (iii) Maria C. Laccotripe Zacharakis ceases to remain or reside in the United States on an H-1 visa.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: October 4, 2003



Harry I. Moatz
Director of Enrollment and Discipline

RECEIVED
CENTRAL FAX CENTER

OCT 06 2003

OFFICIAL